Exhibit 1

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UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

SAN FRANCISCO DIVISION

ARIA DIAGNOSTICS, INC.,

Plaintiff,

vs.

SEQUENOM, INC.,

Defendant.

SEQUENOM, INC.,

Counterclaim Plaintiff,

vs.

ARIA DIAGNOSTICS, INC.,

Counterclaim Defendant,

and

ISIS INNOVATION LIMITED,

Nominal Counterclaim Defendant.

Case No. 3:11-cv-06391-SI

ARIOSA'S [PROPOSED] SUR-REPLY IN OPPOSITION TO SEQUENOM'S MOTION FOR PRELIMINARY INJUNCTION

Date of Hearing: June 29, 2012
Time of Hearing: 9:00 a.m.
Location: Courtroom 10
19th Floor

Judge: Hon. Susan Illston

Ariosa Diagnostics, Inc. respectfully submits this sur-reply for the limited purpose of addressing new testimony on certain core issues of patent invalidity, non-infringement, and harm offered by Sequenom, Inc. for the first time in its reply brief in support of its motion for preliminary injunction.

I. Sequenom's Evidence is Irrelevant to Whether the Asserted Claims Cover Patent-Eligible Subject Matter under Section 101

In a supplemental declaration, Sequenom's expert Dr. Mark Evans argues that there are non-infringing alternatives to the methods claimed in the '540 patent—i.e., "methods to detect cell-free fetal DNA without amplifying the DNA, and without separating maternal blood into a cellular and non-cellular fraction." Supp. Evans Decl. ¶ 25. Dr. Evans fundamentally misunderstands the Supreme Court's decision in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012).

It does not matter whether there are non-infringing alternatives to the methods claimed in the '540 patent for purposes of determining patentability under Section 101. Rather, in *Mayo*, the Supreme Court reiterated its long-held view that a natural phenomenon is never patentable, and that it does not become patentable when combined with "well-understood, routine, conventional activity previously engaged in by researchers in the field." *Mayo*, 132 S. Ct. at 1294. All asserted claims of the '540 patent combine the natural phenomenon of paternally inherited fetal nucleic acid with what, at most, can be described as conventional methods for amplifying and detecting nucleic acid. All of the claims are invalid for that reason. The Supreme Court's admonition against tying up "too much future use" of a natural phenomenon explains in part the *rationale* for its interpretation of Section 101, but it is not itself the test for patentability under Section 101. *Id.* at 1302 ("The presence here of the basic underlying concern that these patents tie up too much future use of laws of nature simply reinforces our conclusion that the processes described in the patents are not patent eligible, while eliminating any temptation to depart from case law precedent.").

It is thus irrelevant whether (as Dr. Evans suggests) there are methods of detecting paternally inherited fetal nucleic acid "that do[] not require amplification," Supp. Evans Decl.

¶ 26, or "that do[] not involve separation of the cellular and non-cellular components of maternal blood," *id*. ¶ 27.[1] There is nothing in *Mayo* to suggest that Section 101 permits the patenting of a natural phenomenon combined with conventional activity already performed by the scientific community at the time of the invention, so long as there is at least some way of using the natural phenomenon not covered by the patented claim. *See Mayo*, 132 S. Ct. at 1294 (requiring an "inventive concept" rather than "well-understood, routine, conventional activity").

Dr. Evans also opines that, "[a]s I have previously described, the approach in the '540 patent was in no way 'conventional."' Supp. Evans Decl. ¶ 28. He provides no support for this statement other than references to paragraphs 20–21, 45, 52–53, and 69–71 of his initial declaration. *Id.* In these paragraphs, Dr. Evans repeatedly makes the point that the applicants were the first to discover the presence of cell-free fetal DNA in maternal plasma and serum. Yet he utterly fails to show that the "*approach* in the '540 patent"—i.e., the activity applied to the natural phenomenon—"was in no way 'conventional.'" *Id.*

In fact, his initial declaration makes clear that just the opposite is true. At paragraph 62, Dr. Evans states that the specification "explains how to perform the invention. It addresses how to prepare the serum or plasma sample, how to extract the nucleic acids, and how to amplify the foetal DNA sequences (using 'standard nucleic acid amplification systems . . . including PCR.'). ('540 patent at 2:19–48.)" Evans Decl. ¶ 62. None of these procedures is new or novel, alone or in combination. Indeed, Dr. Evans admitted as much at his deposition when he agreed that *"traditional DNA diagnostics well before 1997 traditionally involved three steps . . . [s]ample preparation, amplification, and detection" and "others before Dr. Lo amplified and detected nucleic acid in plasma and serum*." Opp. at 6 (quoting Evans Dep. Tr.) (emphasis added). There is nothing in Dr. Evans's original declaration or his supplemental declaration to show that "the steps in the claimed processes (apart from the natural laws themselves)," involve anything other

[1] Although Ariosa takes issue with the evidence that Dr. Evans relies upon to reach his conclusions, it is unnecessary to rebut or otherwise address this evidence because it is simply irrelevant to the patentability analysis under Section 101.

than "well-understood, routine, conventional activity previously engaged in by researchers in the field." *Mayo*, 132 S. Ct. at 1294.

In an effort to overcome these admissions, Sequenom resorts to mischaracterizing Dr. Evans's opinions. In its reply, Sequenom states: "The ability to detect cffDNA, rather than intact fetal cells, in maternal plasma through a fractionation/amplification/detection assay was not known ***at all***" in 1997. Reply at 8:26–9:1 (emphasis in original). By this statement, Sequenom appears to imply that the *scientific activities* used to "detect" cell-free DNA were "not known at all" in 1997. In support of this statement, Sequenom refers to paragraphs 39–40 and 70–73 of Dr. Evans's original declaration. These paragraphs from Dr. Evans's declaration do not say or suggest that *the steps of the asserted claims—alone or in combination*—were anything other than routine and conventional activities in 1997. Rather, these paragraphs of Dr. Evans's declaration discuss that it was difficult for researchers to work with intact fetal cells isolated from maternal blood, and that it was unexpected to find cell-free fetal DNA in maternal plasma or serum (leading researchers to discard the plasma fraction of maternal blood before the applicants' discovery). Dr. Evans's declaration simply reinforces that the only "invention" that the applicants purport to have discovered is the presence of cell-free fetal DNA in maternal plasma and serum.

The discovery of this natural phenomenon is not patentable. Moreover, as explained at length in the expert declaration of Dr. Eric Fearon, the recited steps in the asserted claims of the '540 patent were routine and conventional activities in 1997. Fearon Decl. ¶¶ 58–117. Dr. Evans offers nothing to rebut Dr. Fearon's opinion in his supplemental declaration (or, for that matter, in his original declaration). For these reasons, all asserted claims of the '540 patent are invalid under Section 101.

II. Sequenom Misinterprets and Misapplies Ariosa's Claim Constructions—Ariosa Does Not Detect "Paternally Inherited Nucleic Acid"

Ariosa's construction of "paternally inherited nucleic acid" is "known sequence received only from the father and not fetal sequence which differs from that of the mother"—a construction that flows directly from the specification and prosecution history. Dr. Evans contends that there is a conflict between the first and second parts of Ariosa's construction. Supp. Evans Decl. ¶ 52.

That is incorrect. Dr. Evans fails to appreciate that the first and second parts of Ariosa's claim construction reflect two different *methods* of detecting fetal nucleic acid: (1) a method based on knowing the particular sequence for detection and that the sequence is possessed only by father, and (2) a method based on identifying sequence differences between the fetus and mother. As discussed below, the '540 patent is properly construed to cover *only* the first detection method and to exclude the second detection method.

As to the first part of Ariosa's construction, Dr. Evans states that he "do[es] not see a requirement [in the specification] that the paternally inherited nucleic acid sequence must be known in advance." Supp. Evans Decl. ¶ 49. In offering this opinion, Dr. Evans fails to address the section of the specification entitled "Summary and Objects of the Invention," which states: "The method according to the invention can be applied to the detection of any paternally-inherited sequences *which are not possessed by the mother* . . . ." Bischoff Decl. Ex. 2 at 2:57–59 (emphasis added). Dr. Evans ignores that it is impossible to say whether a sequence is possessed by the father and not by the mother unless it is known in advance. *Id.* ¶ 109. Dr. Evans also ignores that the specification does not disclose or enable any method of determining whether a nucleic acid is of fetal origin other than by reference to a sequence that is known to be received from the father and absent from the mother. *Id.* ¶¶ 103–04.

Nor does Dr. Evans ever come to grips with—or say much of anything about—the prosecution history of the '540 patent. He ignores that, during prosecution, the PTO required the applicants to limit all claims of the '540 patent to "paternally inherited nucleic acid of fetal origin" precisely because the specification only enables "detecting the presence of paternally inherited fetal DNA . . . wherein the fetal DNA is from the Y chromosome and for detecting the presence of the RhD gene in maternal plasma from an RhD negative pregnant wom[a]n . . . ." *Id.* Ex. 10 at 5. These enabling disclosures apply *only* in circumstances where the sequence to be detected is known to come from the father because it is absent from the mother—the detection method covered by Ariosa's construction of the phrase "paternally inherited nucleic acid." Dr. Evans has nothing to say about any of this prosecution history in his supplemental declaration. In short, Ariosa's construction confines the scope of the asserted claims to what the PTO found to be

enabled by the specification. This is entirely proper, particularly where the PTO required the applicants to limit their claims so that they conform to the invention enabled by the specification. *See Standard Oil Co. v. Am. Cyanamid Co.*, 774 F.2d 448, 452 (Fed. Cir. 1985) ("[T]he prosecution history (or file wrapper) limits the interpretation of claims so as to exclude any interpretation that may have been disclaimed or disavowed during prosecution in order to obtain claim allowance.").

In his supplemental declaration, Dr. Evans states that the negative limitation in Ariosa's claim construction—"not fetal sequence which differs from that of the mother"— is incorrect because it would exclude all of the preferred embodiments in the specification. Supp. Evans Decl. ¶ 52. It is certainly true, as Dr. Evans observes, that the experiments described in the specification involve the detection of fetal sequences which differ from that of the mother, such as the detection of a sequence on the Y chromosome (which is not possessed by the mother). The flaw in Dr. Evans's reasoning is his failure to appreciate that the negative limitation is intended to exclude an alternative (and far broader) ***method*** *of detecting fetal nucleic acid*—the detection of "fetal sequence which differs from that of the mother." The applicants enabled the detection of fetal nucleic acid on the Y chromosome *because they knew it was possessed by the father and not by the mother*. The same is true with respect to the detection of the RhD gene in a fetus carried by an RhD negative mother. In contrast, the applicants did not enable a more general method of detecting "fetal sequence which differs from that of the mother." Their failure to enable this different—and broader—method of detecting fetal nucleic acid was the reason that the PTO repeatedly rejected their efforts to secure this claim scope in their continuation application. As the PTO succinctly explained when rejecting the proposed claims, the specification "does not support detecting the presence of a fetal nucleic acid which differs from that of the maternal genome." Bischoff Decl. Ex. 31 at 3.

Accordingly, Ariosa's negative limitation is necessary because, as the PTO recognized during prosecution of the continuation application, methods based on detecting sequence differences between the fetus and the mother are fundamentally different from methods that detect a sequence known to have been received from the father. *Id*. Ex. 31 at 3; Ex. 39 at 6, 10. In the

first method, the sequence to be detected must be known to come from the father (because it is known to be absent from the mother). In the second method, sequence origin is irrelevant—what matters is that the fetal sequence differs from the maternal sequence.

Dr. Evans ignores this critical distinction in his supplemental declaration. Instead, Dr. Evans opines that Ariosa's polymorphic assay, which looks at certain chromosomal loci where fetal sequences are expected to differ from maternal sequences, infringes the asserted claims because detecting paternally inherited nucleic acid is essentially the same thing as detecting sequence differences between the fetus and the mother. Supp. Evans Decl. ¶¶ 70–78.

This opinion is wrong. It is directly contrary to the entire prosecution history of the continuation application, where the applicants sought claims directed to detecting "fetal sequence which differs from that of the mother" precisely because (as discussed in Ariosa's opposition) those claims are broader than, and cover different scope than, claims limited to the detection of "paternally inherited nucleic acid of fetal origin." Opp. at 11–13. Moreover, *the applicants themselves expressly disavowed the very argument that Dr. Evans has advanced in his supplemental declaration.* Specifically, when arguing that their proposed claims would cover detection of a "single nucleotide change" between the fetus and the mother, the applicants explained: "It is immaterial how such a fetal sequence arises; it may be a paternally inherited sequence or it may arise as a result of a spontaneous mutation in either the egg or the sperm. Thus, the invention is not limited to the detection of paternally inherited fetal DNA." Bischoff Decl. Ex. 27 at 13. Given that the applicants themselves made clear that detecting differences between fetal and maternal sequences cannot be treated as equivalent to detecting paternally inherited fetal nucleic acid, it is entirely improper for Dr. Evans to take a different position in his expert opinion. *See Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1576 (Fed. Cir. 1995) ("The prosecution history limits the interpretation of claim terms so as to exclude any interpretation that was disclaimed during prosecution.").

III. Sequenom Mischaracterizes Ariosa's Enablement Defense

Dr. Evans argues that Dr. Fearon "confuses the question of enablement of the asserted claims with the use of those claims for a particular purpose." Supp. Evans Decl. ¶ 31. This is

untrue. As explained at length in the declarations of Dr. Fearon and Dr. Bischoff, the enablement problem with the '540 patent is simple: The claims are not enabled if given the broad construction advanced by Sequenom, irrespective of whether the accused method is for the detection of Down syndrome or some other genetic condition. Fearon Decl. ¶¶ 127–45; Bischoff Decl. ¶¶ 102–13. This is because the specification does not enable the full scope of detecting *any* paternally inherited nucleic acid of fetal origin, as broadly construed by Sequenom. Bischoff Decl. ¶ 102. The PTO itself recognized that the applicants *only* enabled the detection of fetal sequences known to come from the father and not from the mother, such as the detection of Y chromosome sequences or RhD genes in a fetus carried by an RhD negative mother. *Id.* Ex. 10 at 5. Any broader construction is not enabled by the specification.

Recognizing that it has no plausible basis to argue that the specification enables the full scope of the asserted claims under its broad interpretation, Sequenom contends that it is sufficient to enable "some mode" of practicing the claimed invention. Reply at 10:3. The Federal Circuit has squarely rejected this argument. *Auto. Techs. Int'l, Inc. v. BMW of N. Am., Inc.*, 501 F.3d 1274, 1285 (Fed. Cir. 2007) ("We also reject ATI's argument that because the specification enables one mode of practicing the invention, viz., mechanical side impact sensors, the enablement requirement is satisfied. We addressed and rejected a similar argument made in *Liebel-Flarsheim Co. v. Medrad, Inc.*, 481 F.3d 1371 (Fed. Cir. 2007).").

Dr. Evans's citations to subsequent scientific work cannot provide the enablement missing from the specification. The enablement requirement is based on the words of the specification as they would be understood by a person of ordinary skill in the art at the time of the invention. *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1371 (Fed. Cir. 1999). While Dr. Evans contends that the articles show that scientists "used the claimed methods of the '540 patent to detect Down's syndrome," Supp. Evans Decl. ¶ 33, neither Dr. Evans nor the referenced articles suggest that the experimental results were based on the actual teachings of the '540 patent specification.

IV. Sequenom Has Still Not Demonstrated Irreparable Harm

In his supplemental declaration, Sequenom's Senior Vice President William Welch seeks to paint Sequenom and MultiPlan as the underdogs, in a battle over a limited market, against

Ariosa and its partner LabCorp. Supp. Welch Decl. ¶¶ 10–17. But the available market is large, and it is no more than speculation that Sequenom's thriving sales growth since March will somehow vaporize due to Ariosa's agreement with LabCorp. Indeed, the available facts suggest otherwise: Ariosa is a start-up company, whereas Sequenom is an established industry player with international operations. Mr. Welch offers no facts to suggest that MultiPlan somehow will be outmatched by LabCorp in a market that is large enough for Sequenom, Ariosa—and others.

Dated: June 15, 2012

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